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A Brief Review on Obeticholic Acid: the First Farnesoid X Receptor Agonist

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ABSTRACT

Obeticholic acid is a pharmaceutical agent under development used especially to treat liver and gastrointestinal disorders. Its chemical structure is 6 α-ethyl-chenodeoxycholic acid (Figure1). It is a semi synthetic bile acid analogue. In human drug studies, Obeticholic acid is the first farnesoid X receptor agonist and at present, this drug is under phase-II and phase-III clinical trials. Various clinical studies were conducted by using this drug Obeticholic acid to assess the safety and efficacy. In this article, we reviewed the different studies available on Obeticholic acid and its therapeutic use in diseases like non alcoholic steatohepatitis, primary biliary cirrhosis, bile acid malabsorption and portal hypertension.

Keywords: Obeticholic acid, 6 α-ethyl-chenodeoxycholic acid, Farnesoid X receptor agonist.

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INTRODUCTION

Obeticholic acid is a pharmaceutical agent under development used especially to treat liver and gastrointestinal disorders. Its chemical structure is 6 α-ethyl-chenodeoxycholic acid (Figure1). It is a semi synthetic bile acid analogue. In human drug studies, Obeticholic acid is the first farnesoid X receptor agonist and at present, this drug is under phase-II and phase-III clinical trials[1].

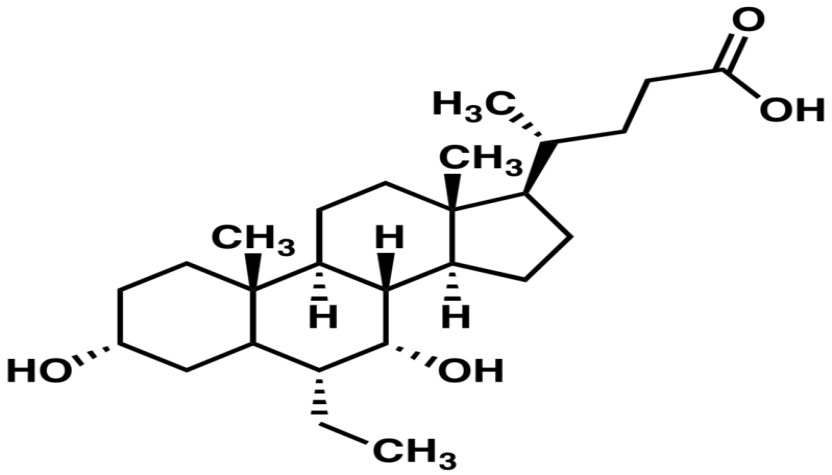

Figure 1: Obeticholic acid (6 α-ethyl-chenodeoxycholic acid)

Chenodeoxycholic acid is a natural bile acid which was identified in the year 1999. It is the most active physiological ligand for the farnesoid X receptor (FXR)[2]. Farnesoid X receptor is a bile acid receptor that involves in bile acid homeostasis, liver fibrosis, intestinal and liver inflammation and cardiovascular disease[3]. Various clinical studies were conducted by using this drug Obeticholic acid to assess the safety and efficacy in different diseases like non alcoholic steatohepatitis, primary biliary cirrhosis, bile acid malabsorption and portal hypertension.

Non Alcoholic Steatohepatitis

Non alcoholic steatohepatitis results from abnormal liver function characterized by fatty liver, fibrosis and inflammation. It often progress to cirrhosis and results in liver transplantation. The drug Obeticholic acid was proposed to treat non alcoholic steatohepatitis also[4]. Obeticholic acid reduces hepatic steatosis and insulin resistance in animal models. Sunder Mudaliar et al., conducted a double blind, placebo controlled, proof of concept study on the efficacy and safety of Obeticholic acid in patients with type-2 diabetes and non alcoholic fatty liver disease. According to a phase-II clinical trial, reduced markers of fibrosis, liver inflammation and enhanced insulin sensitivity were observed with the administration of Obeticholic acid with a dose of 25mg or 50mg daily for 6 weeks[1]. A very recent study revealed that a highly statistically significant improvement was observed in the primary histological end point with no worsening of fibrosis by using this drug Obeticholic acid with a dose of 25mg per day for 72 weeks[5, 6].

Primary Biliary Cirrhosis

Primary biliary cirrhosis is an inflammatory and an auto immune disease characterized by eventual cirrhosis, fibrosis, bile duct injury and cholestasis. Primary biliary cirrhosis may cause jaundice, fatigue and pruritis. When compared to males, primary biliary cirrhosis is more prevalent in females. Treatment with Ursodeoxycholic acid might be beneficial for treating primary biliary cirrhosis but, liver transplantation is required in severe cases. Treatment with farnesoid X receptor agonist could be advantageous in treating the cholestatic diseases like primary biliary cirrhosis based on animal studies. Biochemical benefit was observed during phase-II studies of Obeticholic acid. A significant decrease in serum alkaline phosphatase was observed in a randomized double blind phase-III study with a dose of 5mg or 10mg Obeticholic acid[7, 8, 9].

Bile Acid Malabsorption

The drug Obeticholic acid with a dose of 25mg per day has also shown therapeutic benefits in treating bile acid diarrhoea which is also called as bile acid malabsorption. In bile acid diarrhoea decreased median levels of an ileal hormone (FGF-19) can be observed which regulates the enhanced hepatic bile acid synthesis. This ileal hormone can be effectively stimulated by bile acids and particularly by the drug Obeticholic acid[10, 11].

Portal Hypertension

Len verbeke et al., conducted a study on the drug Obeticholic acid that improves the portal hypertension in cirrhotic rats by two distinct pathways. In this study, bile duct ligated and thioacetamide intoxicated rats were used. Treatment with Obeticholic acid in bile duct ligated and thioacetamide intoxicated rats reactivated the farnesoid X receptor downstream signalling pathway and reduced the portal pressure by decreasing the total intra hepatic vascular resistance without deletorius systemic hypotension. Obeticholic acid enhanced endothelial vasorelaxation capacity in the perfused bile duct ligated and thioacetamide cirrhotic liver and didn't show any hyperresponsiveness. Thus, this drug showed pharmacological benefits in treating the portal hypertension. An open label phase-IIA clinical trial is under process for treating this indication with this drug[3].

CONCLUSION

Obeticholic acid is the first farnesoid X receptor agonist, which is under phase II and III clinical trials at present. Animal studies showed a positive response in treating the liver and gastro intestinal disorders. Some of the Phase II trials for different indications also showed a positive response in treating them. Vast research is required to assess the safety and efficacy of this drug to

promote the drug in the market. Post marketing surveillance is also essential after the entry of the drug into the market which provides prominent information on its benefits and risks.

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